

**FDA Infant Formula GMP Regulation
(Redlined against IFC Suggested Edits¹)**

**Part 106 INFANT FORMULA REQUIREMENTS PERTAINING TO CURRENT
GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES,
QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATION**

106.1 Status and applicability of the regulations in part 106.

106.1(a) The criteria set forth in subparts B, C, and D of this part prescribe the steps that manufacturers must take under section 412(b)(2) and (b)(3) of the Federal Food, Drug, and Cosmetic Act (the act) in processing infant formula. If the processing of the formula does not comply with any regulation in subparts B, C, or D of this part, the formula will be deemed to be adulterated under section 412(a)(3) of the act.

106.1(b) The criteria set forth in subpart E of this part prescribe the quality factor requirements that infant formula must meet under section 412(b)(1) of the act. If the formula fails to comply with any regulation in subpart E of this part, it will be deemed to be adulterated under section 412(a)(2) of the act.

106.1(c) The criteria set forth in subpart F of this part implement the record retention requirements established in section 412(b)(4) of the act. Failure to comply with any regulation in subpart F of this part is a violation of section 301(e) of the act.

106.1(d) The criteria set forth in subpart G of this part describe the circumstances in which infant formula manufacturers are required to register with, submit to, or notify the Food and Drug Administration, and the content of those registrations, submissions, or notifications, under section 412(c), (d), and (e) of the act. Failure to comply with any regulation in subpart G of this part is a violation of section 301(s) of the act.

106.3 Definitions.

106.3(a) Batch means a specific quantity of an infant formula ~~or other material~~ that is intended to have uniform composition, character and quality, ~~within specified limits~~, and is produced according to a master-single manufacturing order during the same cycle of manufacture.

106.3(b) Final-product-stage means the point in the manufacturing process, before distribution of an infant formula, at which the infant formula is homogeneous and is not subject to further degradation due to processing.

¹ Where changes are suggested to the FDA Proposed Regulation, words that IFC suggests deleting are shown by strike-through and words that IFC suggests adding are shown by shading. "Delete or" prior to a paragraph indicates IFC's preference that the language be deleted; the alternative suggested language that follows is provided in case FDA disagrees with the deletion recommendation.

106.3(c) Indicator nutrient means a nutrient whose concentration is measured during the manufacture of an infant formula to confirm complete addition and uniform distribution of a premix or other substance of which the indicator nutrient is a part.

106.3(d) Infant means a person not more than 12 months of age.

106.3(e) Infant formula means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.

106.3(f) In-process batch means a combination of ingredients at any point in the manufacturing process before packaging.

106.3(g) Lot means a batch, ~~or a specifically identified portion of a batch, or other material having uniform composition, character and quality within specified limits;~~ or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform composition, character and quality ~~within specified limits.~~

106.3(h) Lot number, control number, or batch number means any distinctive combination of letters, numbers, symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of infant formula or other material can be determined.

106.3(i) Major change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer. Examples of infant formulas deemed to differ fundamentally in processing or in composition include:

106.3(i)(1) Any infant formula produced by a manufacturer who is entering the U.S. market;

106.3(i)(2) Any infant formula powder processed and introduced for commercial or charitable distribution by a manufacturer who previously only produced liquids (or vice versa);

106.3(i)(3) Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;

106.3(i)(4) Any infant formula manufactured on a new processing line or in a new plant;

106.3(i)(5) Any infant formula manufactured containing a new nutrient constituent not listed in section 412(i) of the act, such as taurine or L-carnitine;

106.3(i)(6) Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., a change from terminal sterilization to aseptic processing); and

106.3(i)(7) An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches).

106.3(j) Minor change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability. Minor changes may or may not affect whether a formula is adulterated under section 412(a) of the Act; changes that affect whether a formula is adulterated under section 412(a) of the Act would require the manufacturer to notify FDA prior to first processing.

106.3(j)(1) Examples of minor changes to infant formulas include:

106.3(j)(1)(i) Reduction of a nutrient that results in a label change, change in a nutrient level which is within 10% of the nutrient levels, minimum or maximum required by Section 412(g) of the FFDCA and is at least 10% closer to the required level;

106.3(j)(1)(ii) Any change in the identity of the ingredients providing nutrients required under section 412 (g) of the Act or trace nutrients added voluntarily consistent with 21 CFR 107.10(b)(5);

106.3(j)(1)(iii) Any design change in the formulation or processing of an infant formula which the manufacturer determines calls for non-routine nutrient testing prior to release, for the purpose of determining whether a possible change has occurred in the levels of nutrients in meeting requirements of Section 412(g) of the Act.

106.3(j)(2) Examples of minor changes to infant formulas that do not require notification prior to first processing include:

106.3(j)(2)(i) Minor reduction of iron level;

106.3(j)(2)(ii) Replacing certain nutrient forms with another form;

106.3(j)(2)(iii) Adjustments in the quantity of a nutrient in a premix or individually added nutrient that results in a specification change for that nutrient in the finished product;

106.3(j)(2)(iv) Changes in time-temperature conditions of preheating during handling of bulk product that cannot reasonably be expected to cause an adverse impact on nutrient levels or nutrient availability;

106.3(j)(2)(v) Changes in oxygen content of a packaged product that might have a minimal effect on the level of nutrients.

106.3(jk) Manufacturer means a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution.

~~106.3(k) Microorganisms means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.~~

106.3(l) New infant formula means:

(1) An infant formula manufactured by a person that has not previously manufactured an infant formula for the U.S. market, and

(2) An infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer.

~~106.3(m) Required Nnutrient means any vitamin, mineral, or other substance or ingredient in infant formula that is required in accordance with the table set out in section 412(i)(1) of by the act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the National Research Council through its development of a Recommended Dietary Allowance or an Estimated Safe and Adequate Daily Dietary Intake range, or that has been identified as essential for infants by the Food and Drug Administration through a Federal Register publication pursuant to the act.~~

106.3(n) Nutrient premix means a combination of ingredients containing two or more nutrients received from a supplier or prepared by an infant formula manufacturer.

~~106.3(o) Quality factors mean those factors necessary to demonstrate the bioavailability of a nutrient and the maintenance of level or potency of nutrients through an expected shelf life of the product that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition.~~

106.3(p) Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled.

106.3(q) Shall is used to state mandatory requirements.

106.3(r) Should is used to state recommended or advisory procedures or to identify recommended equipment.

106.3(s) Responsible party means the manufacturer of an infant formula when all manufacturing steps are performed by a single entity; however, when several entities are

involved in the manufacture of a given formula, it means the manufacturer or other entity that has agreed to assume responsibility for ensuring that all requirements for notification and/or assurance under these regulations are satisfied.

106.3(t) Specifications means quality control limits or standards for raw materials, in-process materials and finished product, which are established by the manufacturer for purposes of controlling quality and consistency for infant formula. Failure to meet an established specification requires a documented review and material disposition decision.

106.3(u) Target Value means quality control limits or standards for raw materials, in-process materials and finished product which are established by the manufacturer for purposes of targeting the manufacturing process to a tight range within broader specifications. Failure to meet an established target value shall result in an immediate review and adjustment, if necessary, during the manufacturing process. No documented review and material disposition is needed when a target value is not met, as long as the established specification is met.

106.3(v) Critical is used to describe systems or equipment that have been designated by the infant formula manufacturer as necessary to control in order to prevent adulteration.

Subpart B--Current Good Manufacturing Practice

106.5 Current good manufacturing practice.

106.5(a) The regulations set forth in this subpart and, for liquid infant formulas, in part 113 of this chapter define the minimum current good manufacturing practices that are to be used in, and the facilities or controls that are to be used for, the manufacture, processing, packing, or holding of an infant formula. Compliance with these provisions is necessary to ensure that such infant formula provides the nutrients required under Sec. 107.100 of this chapter and is manufactured in a manner designed to prevent its adulteration.

106.5(b) The failure to comply with any regulation set forth in this subpart or, for liquid infant formulas, in part 113 of this chapter in the manufacture, processing, packing, or holding of an infant formula shall render such infant formula adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act (the act).

106.6 Production and in-process control system.

106.6(a) Manufacturers shall conform to the requirements of this subpart by implementing a system of production and in-process controls. This production and in-process control system shall cover all those stages of processing, storage and distribution that are under the manufacturer's control, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product, and shall be designed to ensure that all the requirements of this subpart are met.

106.6(b) The production and in-process control system shall be set out in a written plan, or set of procedures, that is designed to ensure that an infant formula is manufactured in a manner that will prevent adulteration of the infant formula.

106.6(c) ~~At any point, step, or stage~~ The manufacturer shall identify the points, steps, or stages in the production process where control is ~~necessary~~ critical to prevent adulteration, ~~the~~. The manufacturer shall, with respect to such points:

106.6(c)(1) Establish ~~standards or specifications~~ and, where appropriate, target values ~~to be met~~;

106.6(c)(2) Monitor the production and in-process control point, step, or stage;

106.6(c)(3) Establish ~~corrective action plans for use when a standard or standard~~ operating procedures to address when a specification established in accordance with paragraph ~~(b)(1)~~ (c)(1) of this section is not met;

106.6(c)(4) Review the results of the monitoring required by paragraph (c)(2) of this section, and review and evaluate ~~the public health significance of any~~ whether deviations from ~~standards or specifications~~ that have been established in accordance with paragraph (c)(1) of this section have public health significance. This review shall be conducted by an individual qualified by training and experience to conduct such reviews; and

106.6(c)(5) Establish Record keeping procedures, in accordance with Sec. 106.100(e)(3), that ensure that compliance with the requirements of this section is documented.

106.10 Controls to prevent adulteration by workers.

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106.10(a) ~~There~~ The manufacturer shall ~~be~~ designate sufficient personnel, qualified by training and experience, to perform all operations, including all required recordkeeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that they are correctly and fully performed.

~~106.10(b) Personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces shall practice good personal hygiene to protect the infant formula against contamination. Good personal hygiene includes, but is not limited to:~~

~~106.10(b)(1) Wearing clean outer garments and, as necessary, protective apparel such as head, face, hands, and arm coverings; and~~

~~106.10(b)(2) Washing hands thoroughly in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated.~~

~~106.10(c) Any person who reports that he or she has, or appears by medical examination or supervisory observation to have, an illness, open lesion, including boils, sores, or infected wounds, or any other source of microbial contamination that creates a reasonable possibility that the safety of an infant formula may be adversely affected, shall be excluded from direct contact with ingredients, containers, closures, in process materials, equipment, utensils, and infant formula product until the condition is corrected or determined by competent medical personnel not to jeopardize the safety of the infant formula.~~

106.20 Controls to prevent adulteration caused by facilities.

106.20(a) Buildings used in the manufacture, processing, packing, or holding of infant formula shall be maintained in a clean and sanitary condition and shall have space for the separation of incompatible operations, such as the handling of raw materials, the manufacture of the product, and packaging and labeling operations.

~~106.20(b) Separate areas shall be designated for holding. A control system shall be established by the manufacturer to control by status the storage and use of raw materials, in-processing materials, and final product finished infant formula. This system shall include the differentiation of the following:~~

~~106.20(b)(1) Pending release for use in infant formula production or pending release of the final product,~~

~~106.20(b)(2) After rejection for use in or as infant formula and before disposition, and~~

~~106.20(b)(3) After release for use in or as infant formula production or after release of the final product.~~

~~106.20(c) Lighting shall allow easy identification of raw materials, packaging, labeling, in process materials, and finished products that have been released for use in infant formula production and shall permit the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis. Any lighting fixtures directly over or adjacent to exposed raw materials, in process materials, or bulk (unpackaged) finished product shall be protected to prevent glass from contaminating the product in the event of breakage.~~

~~106.20(d) Air filtration systems, including prefilters and particulate matter air filters, shall be used on air supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere.~~

~~106.20(e) All rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents shall be stored and used in a manner that protects against contamination of infant formula.~~

106.20(fc)(1) Potable water used in the manufacture of infant formula shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations set forth in 40 CFR part 141, except that the fluoride level of the water used in infant formula manufacturing shall be as low as possible fluoride removal systems shall be employed for fluoridated water supplies. The water shall be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula.

106.20(fc)(2) Manufacturers shall test representative samples of the potable water drawn at a point in the system at which the water is in the same condition that it will be when it is used in infant formula manufacturing.

106.20(fc)(3) Manufacturers shall conduct the tests required by paragraph (f)(2) of this section with sufficient frequency to ensure that the water meets the EPA's Primary Drinking Water Regulations but shall not conduct these tests less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants.

106.20(fc)(4) Manufacturers shall make and retain records, in accordance with §106.100(f)(1), of the frequency and results of testing of the water used in the production of infant formula.

~~106.20(g) There shall be no backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water for infant formula manufacturing.~~

~~106.20(h) When steam comes in direct contact with infant formula, it shall be safe and free of rust and other particulate matter that may contaminate the formula. Boiler water additives in the steam shall be used in accordance with 173.310 of this chapter.~~

106.20(i) Each infant formula manufacturing site shall provide its employees with readily accessible toilet facilities and hand washing facilities that include hot and cold water, soap or detergent, and single service towels and that are maintained in good repair and in a sanitary condition at all times, and that these facilities provide for proper disposal of the sewage. Doors to the toilet facility shall not open into areas where infant formula ingredients, containers, or closures are stored, or where infant formula is processed or stored.

106.30 Controls to prevent adulteration caused by equipment or utensils.

106.30(a) Equipment used in the manufacture, processing, packing or holding of an infant formula shall be of appropriate design and shall be installed to facilitate its intended function and its cleaning and maintenance.

~~106.30(b) Equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula shall be constructed so that surfaces that contact ingredients, in-process materials, or infant formula are made of nontoxic materials and are not reactive or absorptive. Such equipment and utensils shall be designed to be easily cleanable and to withstand the environment of their intended use. All surfaces that contact ingredients, in-process materials, or infant formula shall be cleaned, sanitized, and maintained to protect infant formula from being contaminated by any source. Sanitizing agents used on food contact surfaces must comply with 178.1010 of this chapter.~~

106.30(eb) Manufacturers shall ensure that substances, such as lubricants or coolants, that are required for operation of infant formula manufacturing equipment, but that would render the infant formula adulterated if they contaminated the formula, do not come in contact with formula ingredients, containers, and closures, ~~or in~~ (prior to the closing/sealing operation), or in-process materials or with infant formula itself in a manner not permitted by applicable food additive regulations.

106.30(dc)(1) Manufacturers shall ensure that instruments used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameters at points where control is deemed ~~necessary~~ critical by the infant formula manufacturer to prevent adulteration in the processing of an infant formula are accurate, easily read, properly maintained, and present in sufficient number for their intended use. The instruments and controls shall be tested for accuracy (calibrated) against a known reference standard on or before first use and thereafter at routine intervals, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. The known reference standard shall be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. Manufacturers shall make and retain records of the accuracy checks in accordance with Sec. 106.100(f)(2).

106.30(dc)(2) Instruments and controls that cannot be adjusted to agree with the reference standard shall be repaired or replaced.

106.30(dc)(3) If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard for a point where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and of any actions that need to be taken with respect to that product, shall be made, in accordance with §106.100(f)(2).

106.30(ed)(1) The temperature in cold storage compartments that are used to store raw materials, in-process materials, or final product, and in thermal processing equipment used at points where temperature control is necessary to prevent adulteration, shall be monitored with such frequency as is necessary to ensure that temperature control is maintained.

106.30(ed)(2) Cold storage compartments shall be maintained at a temperature of 40 deg. F (4.4 deg. C), or below confirmed by the manufacturer to assure the quality and safety of in-process materials. 106.30(e)(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.

106.30(ed)(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.

106.30(ed)(3)(ii) Thermal processing equipment shall be equipped with temperature recording devices that will reflect the true temperature on a continuing basis. Cold meet the requirements of 21 C.F.R. Part 113. Temperature monitoring of cold storage compartments shall be equipped with either temperature recording devices that will reflect the true temperature, on a continuing basis, within the compartment or, in lieu of a temperature recording device, a high temperature alarm or a maximum indicating thermometer that has been verified to function properly. If the manufacturer uses either of the latter options, it shall maintain a temperature log in which it notes temperature with such frequency as is necessary to achieve of sufficient frequency to assure proper control. Manufacturers shall make and retain records, in accordance with Sec. 106.100(f)(3), of the temperatures indicated or recorded by these devices.

106.30(e)(4) When a temperature recording device is used, such device shall not read higher than the calibrated temperature indicating device for thermal processing equipment or lower than the reference temperature indicating device for cold storage compartments.

106.30(fe) Equipment and utensils used in an operating production line for the manufacture of infant formula shall be cleaned, and sanitized, and maintained at regular intervals as determined by the manufacturer to be necessary to prevent adulteration of the infant formula. An individual qualified by training or experience to conduct such a review shall check all cleaning, and sanitizing, and maintenance to ensure that it has been satisfactorily completed. Manufacturers shall make and retain records on equipment cleaning, sanitizing, and maintenance, in accordance with Sec. 106.100(f)(4).

106.30(g) Compressed air or other gases that are mechanically introduced into infant formula, that are used to clean any equipment, or that come into contact with any other surface that contacts ingredients, in process materials, or infant formula shall be treated in such a way that their use will not contaminate the infant formula with unlawful indirect food additives or other chemical, physical, or microbiological contaminants. When

~~compressed gases are used at product filling machines to replace air removed from the headspace of containers, the manufacturer shall install a 0.5 micrometer or smaller filter as close to the end of the gas line that feeds gas into the space, as practical.~~

~~106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.~~

~~106.35(a)(1) For the purposes of this section, "hardware" means all automatic equipment, including mechanical and electronic equipment (including computers), that is used in production or quality control of a infant formula.~~

~~106.35(a)(2) For the purposes of this section, "software" means any programs, procedures, rules, and associated documentation used in the operation of a system.~~

~~106.35(a)(3) For the purposes of this section, "system" means a collection of components (including software and hardware) organized to accomplish a specific function or set of functions in a specified environment.~~

~~106.35(a)(4) For the purposes of this section, "validation" means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics.~~

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106.35(ba)(1) All critical systems shall be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing or analyzing infant formula in accordance with this subpart and subpart C of this part.

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106.35(ba)(2) The infant formula manufacturer shall ensure that critical hardware is routinely ~~calibrated~~, inspected, and checked according to written procedures.

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106.35(ba)(3) The infant formula manufacturer shall check and document the accuracy of input into, and output generated by, any critical system used in the production or quality control of an infant formula. The degree and frequency of input/output verification shall be based on the manufacturer's assessment of the complexity and reliability of the system and the level of risk associated with the safe operation of the system. Quality evaluations should be used to substantiate the adequacy of the checks required by this section.

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106.35(ba)(4) The infant formula manufacturer shall ensure that all critical systems are ~~validated before their first use to manufacture~~ checked as per 106.35(b)(3) before the release of commercial product initially manufactured with these systems.

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106.35(ba)(5) The infant formula manufacturer shall ensure that any critical system that is modified is ~~revalidated~~ reassessed after the modification and before ~~use of release of~~ any infant formula manufactured with the modified system ~~to manufacture commercial product~~. All modifications to critical software shall be made by a designated individual and shall be checked by the infant formula manufacturer to ensure that infant formula that is produced or analyzed using the modified software complies with this subpart and with subpart C of this part.

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106.35(eb) The infant formula manufacturer shall make and retain necessary records, in accordance with Sec. 106.100(f)(5), concerning critical automatic (mechanical or electronic) equipment.

106.40 Controls to prevent adulteration caused by ingredients, containers, and closures.

~~106.40(a) The only substances that may be used in infant formulas are food ingredients whose use in infant formula is safe and suitable under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act; that is, the substance is generally recognized as safe (GRAS) for such use, is used in accordance with the agency's food additive regulations, or is authorized by a prior sanction.~~

~~106.40(b) Infant formula containers and closures shall not be reactive or absorptive so as to affect the safety of the infant formula, and all packaging material that comes in contact with infant formula shall be composed of substances that are GRAS for use in or on food, GRAS for their intended use in food packaging, authorized by a prior sanction issued by the agency, or authorized for use as an indirect food additive. Any packaging material that comes in contact with infant formula shall be used in accordance with any prescribed limitations.~~

106.40(ea) Ingredients, containers, and closures used in the manufacture of infant formula shall be identified with a batch or lot number to be used in recording their disposition.

106.40(db) Infant formula manufacturers shall develop written specifications for ~~their acceptance or rejection of~~ ingredients, containers, and closures used as components in infant formula manufacture. ~~These specifications shall stipulate the standards for~~

~~acceptance or rejection of such ingredients, containers, and closures as well as the procedures for determining whether the ingredients, containers, and closures meet that standard. An individual qualified by training or experience shall conduct an investigation of a finding that any ingredients, containers, or closures used in a batch of infant formula failed to meet any of the manufacturer's specifications and packaging.~~

106.40(ec) Ingredients, containers and closures shall be ~~stored in areas~~ controlled by a system that clearly ~~designated for~~ designates:

106.40(ec)(1) Materials pending release for use,

106.40(ec)(2) Materials released for use, or

106.40(ec)(3) Materials rejected for use in infant formula production. Any lot of ingredients, containers, or closures that ~~does not meet the manufacturer's specifications~~ shall be rejected and has been rejected shall be controlled under a quarantine system designed to prevent its use in the manufacture of infant formula, unless and until it is disposed of or reconditioned and found acceptable.

106.40(fd) If the manufacturer determines that an ingredient, a container, or a closure that has been tested and examined is exposed to ~~air, heat, or other~~ conditions that may ~~could~~ be expected to adversely affect it, the ingredient, container, or closure shall be retested or reexamined to ensure ~~that it still meets the manufacturer's specifications.~~ its acceptability for use in the manufacturing process.

106.40(ge) Manufacturers shall make and retain records, in accordance with §106.100(f)(6), on the ingredients, containers, and closures used in the manufacture of infant formula.

106.50 Controls to prevent adulteration during manufacturing.

106.50(a)(1) Manufacturers shall prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula.

106.50(a)(2) The manufacturer shall make and retain records, in accordance with §106.100(e), that include complete information relating to the production and control of the batch. An individual qualified by training or experience shall conduct an investigation of any deviations from the master manufacturing order and any corrective actions taken.

106.50(a)(3) Changes made to the master manufacturing order shall be drafted, reviewed, and approved by a responsible official and include an evaluation of the effect of the change on the nutrient content and the suitability of the formula for infants.

106.50(b) The manufacturer shall establish controls to ensure that each raw or in-process ingredient required by the master manufacturing order is examined by one person and checked by a second person or system. This checking will ensure that the correct

ingredient is added during the manufacturing process, that the ingredient has been released for use in infant formula, and that the correct weight or measure of the ingredient is added to the batch.

106.50(c) The manufacturer shall ~~identify the contents, including the processing stage and the lot or batch number of a batch of infant formula, of all compounding and storage containers, processing lines, and major equipment~~ establish a system that permits it to determine the major equipment systems used during the production of a batch of an infant formula.

106.50(d) The manufacturer shall establish and document a system of controls to ensure that the nutrient levels required by Sec. 107.100 of this chapter are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants. ~~Such controls shall include but not be limited to:~~

~~106.50(d)(1) The mixing time; the speed, temperature, and flow rate of product; and other critical parameters necessary to ensure the addition of required ingredients to, and the homogeneity of, the formula;~~

~~106.50(d)(2) The spray drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial and other contamination;~~

~~106.50(d)(3) The removal of air from the finished product to ensure that nutrient deterioration does not occur;~~

~~106.50(d)(4) Ensuring that each container of finished product is properly sealed. Such controls shall involve use of established procedures, specifications, and intervals of examination that are designed by qualified individuals and are sufficient to:~~

~~106.50(d)(4)(i) Detect visible closure or seal defects, and~~

~~106.50(d)(4)(ii) Determine closure strength through destructive testing. Manufacturers of liquid infant formulas, which are thermally processed low acid foods packaged in hermetically sealed containers, shall perform such closure integrity testing in accordance with 113.60(a) of this chapter.~~

106.50(e) The manufacturer shall establish controls that ensure that the equipment used at points where control is deemed necessary to prevent adulteration is monitored, so that personnel will be alerted to malfunctions.

106.50(f) The manufacturer shall establish controls that ensure that rejected in-process materials:

106.50(f)(1) Are clearly identified as having been rejected for use in an infant formula;

106.50(f)(2) Are controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable;

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106.50(f)(3) If subjected to reprocessing, ~~M~~meet the appropriate specifications, ~~if reprocessed~~, or undergo a documented material disposition decision before being released for further use in infant formula.

106.55 Controls to prevent adulteration from microorganisms.

106.55(a) Manufacturers of liquid infant formula shall comply with the procedures specified in part 113 of this chapter for liquid infant formula.

106.55(b) Manufacturers of powdered infant formula shall test representative samples of every batch of the formula at the final product stage, before distribution, to ensure that the infant formula meets the microbiological quality standards listed in paragraph (c) of this section.

106.55(c) Any powdered infant formula that contains any microorganism that exceeds the M value listed for that microorganism in Table 1 of this section will be deemed to be adulterated under sections 402 and 412 of the Federal Food, Drug, and Cosmetic Act (the act). FDA will determine compliance with the M values listed below using the Bacteriological Analytical Manual (BAM), 8th ed. (1995), published by the AOAC International Association of Official Analytical Chemists, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20877, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW, rm. 3321, Washington, DC, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Suite 700, Washington, DC.

Microorganism	M Value ¹
Aerobic Plate Count (APC)	10,000 CFU/gram (g). ²
Enterobacteriaceae (EB) ³	3.05 MPN/g. ^{4,5}
Fecal coliforms ⁶	3.05 MPN/g. 0. ⁷
<i>Salmonella</i>	0. ⁷
<i>Listeria monocytogenes</i>	0. ⁷
<i>Staphylococcus aureus</i>	3.05 MPN/g.
<i>Bacillus cereus</i> ⁸	100 1000 CFU/g.

¹ The M value is the maximum allowable number of microorganisms present in 1 g of dry infant formula.
² CFU/g, colony forming units per g. Probiotic infant formulas are exempted.
³ M values for EB ~~coliforms~~ greater than or equal to 3.05 are not violative if ~~testing for fecal coliforms are not confirmed in the EB test results in an M value equal to or less than 3.05.~~
⁴ MPN/g, most probable number per g.
⁵ The MPN value of 3.05 in this table is derived from the tables of calculated MPN values that appear in the January 2001 revision of the 8th ed. of the BAM when using an inoculation series of 0.1, 0.01, and 0.001g (or ml) of the infant formula sample.
⁶ No confirmation testing for fecal coliforms is required when the M value for EB ~~coliforms~~ is less than ~~or equal to~~ 3.05.
⁷ None detected.
⁸ *B. cereus* testing must be performed only if the APC exceeds 1000 ~~100~~ CFU/g (except for probiotic infant formulas).

106.55(d) Manufacturers shall make and retain records, in accordance with §106.100(e)(5)(ii) and (f)(7), on the testing of infant formulas for microorganisms.

106.60 Controls to prevent adulteration during packaging and labeling of infant formula.

106.60(a) Manufacturers shall examine packaged and labeled infant formula during finishing operations to ensure that containers and packages in the lot have the correct label, the correct use-by date, and the correct code established under §106.80.

106.60(b) Labels shall be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, and distribution, ~~and use.~~

106.60(c) ~~All infant formulas held in a single package shall be the same product bearing the same code, established under Sec. 106.80.~~ Packaging used to hold multiple containers of the same type of infant formula shall be labeled with the product name, the name of the manufacturer, distributor or shipper, and the lot number. Packaging used to hold containers of different types of infant formula shall be labeled with the product names, the name of the manufacturer, responsible party or shipper, a lot number code that can serve to identify the contents, and an expiration date reflecting a shelf life no greater than the container exhibiting the shortest expiration date.

106.70 Controls on the release of finished infant formula.

106.70(a) The manufacturer or responsible party shall hold, or maintain under its control, each batch of infant formula until it determines that the batch meets ~~all of its specifications, including those adopted to meet the requirements of 106.55 on microbiological contamination and 106.91(a) on quality control procedures, and releases the batch for distribution.~~ 21 CFR Part 106.

106.70(b) Each batch of infant formula that fails to meet the ~~manufacturer's specifications~~ requirements of Sec. 106.70(a) shall be rejected. Although the batch may be reprocessed, any batch of infant formula that is reprocessed shall be shown to meet the requirements of Sec. 106.70(a) before it is released.

106.70(c) An individual qualified by training or experience shall conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's ~~specifications~~ or responsible party's specifications in order to ensure that such failure does not lead to the release of adulterated product.

106.80 Traceability.

106.80(a) Manufacturers shall ensure traceability by coding infant formulas in conformity with the coding requirements prescribed in §113.60(c) of this chapter for thermally processed low-acid foods packaged in hermetically-sealed containers, except as provided in paragraph (b) of this section.

106.80(b) Batches of powdered infant formula that are manufactured in stages over more than 1 day, in lieu of being coded in accordance with §113.60(c) of this chapter, may be coded with a sequential number that identifies the product and the establishment where the product was packed and that permits tracing of all stages of manufacture of that batch, including the year, the days of the year, and the period during those days that the product was packed, and the receipt and handling of raw materials used.

106.90 Audits of current good manufacturing practice.

Manufacturers of an infant formula, or an agent of such manufacturers, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable ~~in all aspects~~ of infant formula production and of the agency's regulations concerning good manufacturing practices but who has no direct responsibility for the matters being audited.

Subpart C--Quality Control Procedures

106.91 General quality control.

106.91(a) *Nutrient testing to ensure that each batch of infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test each batch as follows:

106.91(a)(1) Each nutrient premix used in the manufacture of an infant formula shall be tested for each nutrient that the manufacturer is relying on the premix to provide to ensure that the premix is in compliance with the manufacturer's specifications;

106.91(a)(2) During the manufacturing process, after the addition of the premix, or at the final-product-stage but before distribution, each batch of infant formula shall be tested for at least one indicator nutrient for each of the nutrient premixes used in the infant formula to confirm that the nutrients supplied by each of the premixes are present, in the proper concentration, in the batch of infant formula.

106.91(a)(3) At the final-product-stage, before distribution of an infant formula, each batch shall be tested for vitamins A, C, E, and thiamin.

106.91(a)(4) During the manufacturing process or at the final-product-stage, before distribution, each batch shall be tested for ~~all nutrients~~ each nutrient required to be included in such formula under 107.100 of this chapter ~~and for any nutrient added by the manufacturer for which testing is not~~ if the presence of that nutrient in the batch has not been confirmed pursuant to testing conducted for compliance with paragraphs (a)(1), (a)(2) or (a)(3) of this section. Such testing shall be conducted using validated test methods.

106.91(b) ~~Stability testing~~ *Testing of finished product to confirm that the infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test finished product as follows:

106.91(b)(1) *Periodic Analysis.* Every 3 months, manufacturers or responsible parties shall collect representative samples ~~from the final-product-stage~~ of infant formula of one batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each manufacturing facility. The manufacturer shall test these samples for each nutrient required under Sec. 107.100 of this chapter ~~and for any nutrient added by the manufacturer.~~ The frequency of such testing shall be at the beginning, midpoint, and end of that was not tested directly at the finished product stage pursuant to 106.91(a)(4).

106.91(b)(2) *Stability testing.* Using representative samples collected from finished product batches, the manufacturer shall conduct stability analysis for selected labile nutrients ~~The frequency of such testing shall be at the beginning, midpoint, and end of~~ with sufficient frequency to substantiate the maintenance of nutrient content consistent throughout the shelf life of the infant formula ~~and, depending on the nutrient and its stability within the matrix of the formulation, with additional frequency as is necessary to ensure that such formula complies with section 412 of the Federal Food, Drug, and Cosmetic Act (the act) throughout the shelf life of the infant formula.; except that:~~

106.91(b)(43) If the infant formula is a new infant formula, manufacturers or responsible parties shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the new infant formula and test these samples according to the requirements of this section; and

106.91(b)(24) If an infant formula has been changed in formulation or in processing in a way that does not make it a new infant formula but that may affect whether it is

adulterated under section 412(a) of the act, the manufacturer or responsible party shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the infant formula and shall test these samples according to the frequency required by this section for each nutrient that has been or may have been significantly and adversely affected by the change. The manufacturer or responsible party shall determine if stability testing should be conducted for such a change and the frequency of such testing, if deemed necessary.

106.91(c) Quality control records. Manufacturers shall make and retain quality control records in accordance with Sec. 106.100(e)(5)(i) and (f)(7).

106.92 Audits of quality control procedures.

A manufacturer of an infant formula, or an agent of such a manufacturer thereof, shall conduct regularly scheduled audits, according to its established practice, to determine whether the manufacturer has complied with the quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act and is manufactured in a manner designed to prevent adulteration of the infant formula under section 412(a)(1) and (a)(3) of the Federal Food, Drug, and Cosmetic Act. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning quality control procedures but who has no direct responsibility for the matters being audited.

Subpart D--Conduct of Audits.

106.94 Audit plans and procedures.

106.94(a) Manufacturers shall develop and follow a written audit plan that is available at the manufacturing facility for FDA inspection.

106.94(b) The audit plan shall include audit procedures that set out the methods the manufacturer or responsible party uses to determine whether the facility is operating in accordance with current good manufacturing practice, with the quality control procedures that are necessary to assure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act, and in a manner designed to prevent adulteration of the infant formula.

106.94(c) The audit procedures shall include, but not be limited to:

106.94(c)(1) An evaluation of the production and in-process control system established under Sec. 106.6(b) by:

106.94(c)(1)(i) Observing the ~~production~~ critical manufacturing steps of infant formula and comparing the observed process to the written production and in-process control plan required under Sec. 106.6(b);

106.94(c)(1)(ii) Reviewing records of representative batches, over multiple days of production, of the monitoring of points, steps, or stages where control is ~~deemed~~ necessary critical to prevent adulteration; and

106.94(c)(1)(iii) Reviewing records of how deviations from any ~~standard or~~ specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled to assure that the review was complete; and

106.94(c)(2) A review of a representative sample of all records maintained in accordance with Sec. 106.100(e) and (f).

Subpart E--Quality Factors for Infant Formulas

106.96 Quality factors in infant formulas.

106.96(a) All infant formulas shall meet established quality factors, ~~when fed to infants as a sole source of nutrition, be of sufficient quality to meet the nutritional requirements for healthy growth. The regulations set forth in this subpart define the minimum quality factors for infant formulas.~~

~~106.96(b) All infant formulas shall be capable of supporting normal physical growth of infants.~~

106.96(eb) All infant formulas shall be formulated and manufactured such that the protein is of sufficient biological quality to meet the protein requirements of infants.

106.97 Assurances for quality factors.

~~106.97(a) General quality factor of normal physical growth.~~

~~106.97(a)(1) The manufacturer shall conduct an adequate and well-controlled clinical study, in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition.~~

~~106.97(a)(1)(i) The manufacturer shall:~~

~~106.97(a)(1)(i)(A) Conduct a clinical study that is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study.~~

~~106.97(a)(1)(i)(B) Collect and maintain data in the study on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and~~

average daily weight increment, and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves. The NCHS growth charts are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Constituent Operations (HFS-565), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, may be examined at the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or the Office of the Federal Register, 800 North Capitol St. NW, Suite 700, Washington, DC.

~~106.97(a)(1)(i)(C) Collect anthropometric measurements at the beginning of the clinical study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the conclusion of the study.~~

~~106.97(a)(1)(ii) The clinical study protocol should:~~

~~106.97(a)(1)(ii)(A) Describe the scientific basis and objectives of the study, the planned control and treatment feeding regimens, the entrance criteria used to enroll infants in the study, the method of randomization used for the assignment of infants to feeding groups, the collection of specific measurements and other data, the methods used to limit sources of bias, and the planned methods of statistical analysis;~~

~~106.97(a)(1)(ii)(B) Describe the necessary qualifications and experience of investigators;~~

~~106.97(a)(1)(ii)(C) Be reviewed and approved by an Institutional Review Board (IRB) in accordance with part 56 of this chapter. The manufacturer shall establish procedures to obtain written informed consent from parents or legal representatives of the infants enrolled in the study in accordance with part 50 of this chapter;~~

~~106.97(a)(1)(ii)(D) Explain how the study population represents the population for which the new infant formula is intended and how the study addresses the intended conditions of use of the formula.~~

~~106.97(a)(1)(ii)(E) Describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design;~~

~~106.97(a)(1)(ii)(F) Describe the plan to identify and evaluate any adverse effects;~~

~~106.97(a)(1)(ii)(G) Describe the quality control procedures used to ensure the validity and reliability of the measurements collected.~~

~~106.97(a)(1)(ii)(H) Describe and compare the composition of the test and control formulas.~~

~~106.97(a)(1)(ii)(I) Describe the basis upon which the test formula is appropriate for use in evaluating the formula that the manufacturer intends to market, if the test formula used in a study is not identical to the formula that is intended to be marketed in the United States.~~

~~106.97(a)(2) The manufacturer may request an exemption from the requirements of paragraph (a)(1) of this section if:~~

~~106.97(a)(2)(i) The manufacturer has similar experience using an ingredient, an ingredient mixture, or a processing method in the production of an infant formula marketed in the United States and can demonstrate that infant formula made with that ingredient, ingredient mixture, or processing method meets the quality factor requirements in Sec. 106.96;~~

~~106.97(a)(2)(ii) The manufacturer markets a formulation in more than one form (e.g., liquid and powdered forms) and can demonstrate that the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability;~~

~~106.97(a)(2)(iii) The manufacturer can demonstrate that the requirements of paragraph (a)(1) of this section are not appropriate for evaluation of a specific infant formula, and that an alternative method or study design for showing that the formula supports healthy growth in infants fed it as their sole source of nutrition is available.~~

106.97(ba) Specific quality factor for protein quality of infant formula.

106.97(ba)(1) The manufacturer or responsible party shall collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants. The manufacturer or responsible party shall establish the biological quality of the protein in its infant formula with any AOAC approved method, including by demonstrating that the protein source supports adequate growth using the Protein Efficiency Ratio (PER) rat bioassay described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., sections 43.3.04 and 43.3.05, "AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay" which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20857, or the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Washington, DC. If the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended.

106.97(ba)(2) The manufacturer may request an exemption from the requirements of paragraph (b)(1) of this section if:

106.97(ba)(2)(i) The protein source, including any processing method used to produce the protein source, is already used in another infant formula marketed in the United States, manufactured by the same manufacturer, and the manufacturer can demonstrate that such infant formula meets the quality factor requirements prescribed in Sec. 106.96;

106.97(ba)(2)(ii) The protein source, including any processing methods used to produce the protein source, is not a major change from the infant formula it replaces, and the manufacturer can demonstrate that the infant formula it replaces meets the quality factor requirements prescribed in Sec. 106.96.

In newly redesignated subpart F, Sec 106.100 is amended by revising paragraphs (e), (f), (g), (j) and (k)(3), and by removing and reserving paragraph (h) to read as follows:

106.100 Records

* * * *

106.100(e) *Batch production and control records.* For each batch of infant formula, manufacturers shall prepare and maintain records that include complete information relating to the production and control of the batch. ~~These records shall include but are not limited to:~~ The records that are necessary under this paragraph are:

106.100(e)(1) The master manufacturing order. The master manufacturing order shall include ~~but is not limited to:~~

106.100(e)(1)(i) The significant steps in the production of the batch and the date on which each significant step occurred;

106.100(e)(1)(ii) The identity of the major equipment and processing lines systems used in producing the batch, if the plant in which the formula is made includes more than one set of equipment or more than one processing line system;

106.100(e)(1)(iii) The identity of each batch or lot of ingredients, containers, and closures used in producing the batch of formula;

106.100(e)(1)(iv) The amount of each ingredient to be added to the batch of infant formula and a check (verification) that the correct amount was added; and

106.100(e)(1)(v) Copies of all labeling primary container labels used and the results of examinations conducted during the finishing operations to provide assurance that containers and packages in the lot have the correct label.

106.100(e)(2) Any deviations from the master manufacturing order and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation ~~because of the deviations.~~

106.100(e)(3) Documentation, in accordance with Sec. 106.6(c), of the monitoring at any point, step, or stage in their production process where control is deemed ~~necessary~~ critical

to prevent adulteration. ~~These records~~ The records that are necessary under this paragraph shall include, ~~but not be limited to:~~

106.100(e)(3)(i) A list of the ~~standards or~~ specifications established at each point, step, or stage in their production process where control is deemed necessary ~~to prevent adulteration including documentation of the scientific basis for each standard or specification;~~ by the manufacturer.

106.100(e)(3)(ii) The actual values obtained during the monitoring operation, any deviations from established ~~standards or~~ specifications, and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation;

106.100(e)(3)(iii) Identification of the person monitoring each point, step, or stage in their production process where control is deemed necessary to prevent adulteration.

106.100(e)(4) The conclusions and follow-up, along with the identity, of the individual qualified by training or experience who investigated:

106.100(e)(4)(i) Any deviation from the master manufacturing order and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation;

106.100(e)(4)(ii) A finding that a batch or any of its ingredients failed to meet the infant formula manufacturer's specifications; and

~~106.100(e)(4)(iii) A failure to meet any specification or standard at any point, step, or stage in the production process where control is deemed necessary to prevent adulteration.~~

106.100(e)(5) The results of all testing performed on the batch of infant formula, including testing on the in-process batch, at the final-product stage, and on finished ~~product throughout the shelf life of the product.~~ The results recorded shall include ~~but are not limited to:~~

106.100(e)(5)(i) The results of all quality control testing conducted, in accordance with Sec. 106.91(a) and (b), to verify that each nutrient required by Sec. 107.100 of this chapter is present in each batch of infant formula at the level required by Sec. 107.100, and that any nutrient added by the manufacturer is present at the appropriate level with:

106.100(e)(5)(i)(A) A summary table identifying the stages of the manufacturing process at which the nutrient analysis for each required nutrient under §106.91(a) is conducted, and

~~106.100(e)(5)(i)(B) A summary table on the stability testing program, including the nutrients tested and the frequency of testing of nutrients throughout the shelf life of the product under 106.91(b); and~~

106.100(e)(5)(ii) For powdered infant formula, the results of any testing conducted in accordance with §106.55(b) to verify compliance with the microbiological quality standards in §106.55(c).

106.100(f) Manufacturers shall make and retain all the following necessary records pertaining to current good manufacturing practice as described in subpart B of this part, ~~including but not limited to:~~

106.100(f)(1) Records, in accordance with §106.20(f)(3), of the frequency and results of testing of the water used in the production of infant formula;

106.100(f)(2) Records, in accordance with §106.30(d), of accuracy checks of instruments and controls. A certification of accuracy of any known reference standard used and a history of recertification shall be maintained. At a minimum, such records shall specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test. If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification ~~or standard~~ at a point, step, or stage in the production process where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and any actions that need to be taken with respect to that product, shall be made.

106.100(f)(3) Records, in accordance with §106.30(e)(3)(ii), of the temperatures monitored for cold storage compartments and thermal processing equipment.

106.100(f)(4) Records, in accordance with Sec. 106.30(f), on equipment cleaning, sanitizing, and critical maintenance that show the date and time of such cleaning, sanitizing, and critical maintenance ~~and the lot number of each batch of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance~~. The person performing and checking the cleaning, sanitizing, and critical maintenance shall date and sign or initial the record indicating that the work was performed.

Delete
or

106.100(f)(5) Records, in accordance with Sec. 106.35(c), on all automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. These records shall include ~~but not be limited to:~~

~~106.100(f)(5)(i) A list of all systems used with a description of computer files and the inherent limitations of each system;~~

~~106.100(f)(5)(ii) A copy of all software used;~~

~~106.100(f)(5)(iii) Records that document installation, calibration, testing or validation, and maintenance of the systems used;~~

~~106.100(f)(5)(iv) A list of all persons authorized to create or modify software;~~

~~106.100(f)(5)(v) Records that document modifications to software, including the identity of the person who modified the software;~~

~~106.100(f)(5)(vi) Records that document retesting or revalidation of modified systems; and~~

~~106.100(f)(5)(vii) A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate diskettes, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss.~~

106.100(f)(6) Records, in accordance with 106.40(g), on ingredients, containers, and closures used in the manufacture of infant formula. The records that are necessary under this paragraph are ~~These records shall include, but are not limited to:~~

106.100(f)(6)(i) The identity and quantity of each lot of ingredients, containers, and closures;

106.100(f)(6)(ii) The name of the supplier;

106.100(f)(6)(iii) The supplier's lot numbers;

106.100(f)(6)(iv) The name and location of the manufacturer of the ingredient, container, and closure, if different from the supplier;

106.100(f)(6)(v) The date of receipt;

106.100(f)(6)(vi) The receiving code as specified; and

106.100(f)(6)(vii) The results of any test or examination (including retesting and reexamination) performed on the ingredients, containers, and closures and the conclusions derived therefrom and the disposition of all ingredients, containers, or closures.

106.100(f)(7) A full description of the methodology used to test powdered infant formula to verify compliance with the microbiological quality standards of §106.55(c) and the methodology used to do quality control testing, in accordance with §106.91(a) and (b).

106.100(f)(8) Results of stability testing performed pursuant to 106.91(b)(2).

106.100(g) The manufacturer shall maintain all records pertaining to the manufacturer's distribution of the infant formula, including records ~~that show that for products produced for export only are exported. Such records shall include, but not be limited to, all.~~ The records required under this paragraph are those providing the information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107 of this chapter.

106.100(h) [Reserved]

* * * * *

106.100(j) The manufacturer shall make and retain records pertaining to regularly scheduled audits, including the audit plans and procedures, the findings of the audit, and a listing of any changes made in response to these findings. The manufacturer shall make readily available for authorized inspection the audit plans and procedures and a statement of assurance that the regularly scheduled audits are being conducted. The findings of the audit and any changes made in response to these findings shall be maintained for the time period required under §106.100(n), but need not be made available to FDA.

106.100(k)(3) When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the ~~manufacturer~~ responsible party shall, within 15 days of receiving such information, conduct an investigation and notify the agency as required in Sec. 106.150.

Subpart G--Registration, Submission, and Notification Requirements

106.110 New infant formula registration.

106.110(a) Before a new infant formula may be introduced or delivered for introduction into interstate commerce, the manufacturer of such formula shall register with the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204. An original and two copies of this registration shall be submitted.

106.110(b) The new infant formula registration shall include:

106.110(b)(1) The name of the new infant formula,

106.110(b)(2) The name of the manufacturer and of the responsible party if other than the manufacturer,

106.110(b)(3) The place of business of the manufacturer, and of the responsible party if other than the manufacturer, and

106.110(b)(4) ~~All~~ The names and addresses of all establishments at which the manufacturer or responsible party intends to manufacture such new infant formula.

106.120 New infant formula submission.

106.120(a) At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a ~~manufacturer~~ responsible party shall submit notice of its intent to do so to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies of the notice of its intent to do so shall be submitted.

106.120(b) The new infant formula submission shall include:

106.120(b)(1) The name and physical form (e.g., powder, ready-to feed, or concentrate) of the infant formula;

106.120(b)(2) An explanation of why the formula is a new infant formula;

106.120(b)(3) The quantitative formulation of each form of the infant formula that is the subject of the notice in units per volume (for liquid formulas) or units per dry weight (for powdered formulas). When applicable, the submission shall include a description of any reformulation of the infant formula, including a listing of each new or changed ingredient and a discussion of the effect of such changes on the nutrient levels in the formulation;

106.120(b)(4) A description, when applicable, of any change in processing of the infant formula. ~~Such description shall identify the specific change in processing, including side-by-side, detailed schematic diagrams comparing the new processing to the previous processing (including processing times and temperatures);~~

106.120(b)(5) Assurance that the infant formula will not be marketed unless the formula meets the quality factor requirements of section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and the nutrient content requirements of section 412(i) of the act.

106.120(b)(5)(i) Assurance that the formula meets the quality factor requirements, which are set forth in subpart E of this part, shall be provided by a submission that complies with Sec. 106.121.

106.120(b)(5)(ii) Assurance that the formula complies with the nutrient content requirements, which are set forth in §107.100 of this chapter, shall be provided by a statement assuring that the formula will not be marketed unless it meets the nutrient requirements of §107.100 of this chapter, as demonstrated by testing required under subpart C of this part;

106.120(b)(6) Assurance that the processing of the infant formula complies with section 412(b)(2) of the act. Such assurance shall include but not be limited to:

106.120(b)(6)(i) A responsible party that has not previously manufactured infant formula for sale in the U.S. market must support the premarket notification with a clinical study.

106.120(b)(6)(ii) Clinical studies also may be necessary when a current manufacturer or responsible party predicts, based on its experience or theory, that a major change could have possible significant adverse impact on bioavailability of nutrients and when chemical testing or other scientific information are unavailable to rule out such an adverse impact.

106.120(b)(6)(iii) The manufacturer shall determine the scope, degree and complexity of any needed clinical testing, on a case-by-case basis. The particular elements of the study shall take into account Guidelines issued by FDA regarding clinical study protocol and design and endpoints needed to support potential claims.

106.120(b)(67) Assurance that the processing of the infant formula complies with section 412(b)(2) of the act. Such assurance shall include but not be limited to:

106.120(b)(67)(i) A statement that the formula will be produced in accordance with subparts B and C of this part;

~~106.120(b)(6)(ii) The basis on which each ingredient meets the requirements of 106.40(a), e.g., that it is an approved food additive, that it is authorized by a prior sanction issued by the agency, or that it is GRAS for its intended use. Any claim that an ingredient is GRAS shall be supported by a citation to the agency's regulations or by an explanation, including a list of published studies and a copy of those publications, for why, based on the published studies, there is general recognition of the safety of the use of the ingredient in infant formula.~~

106.120(c) For products for export only and in compliance with Section 801(e) of the Act, the information under paragraph (b) of this section is not required and need not be submitted; a manufacturer may submit, in lieu of the information required under paragraph (b) of this section, a statement that the infant formula meets the specifications of the foreign purchaser, does not conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package to indicate that it is intended for export only, and will not be sold or offered for sale in domestic commerce.

106.120(d) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will notify the submitter within 10 working days if the notice is not adequate complete because it does not meet the requirements of section 412(c) and (d) of the act.

106.120(e) If a new infant formula submission is adequate complete and includes all requirements of 106.120(b), FDA will acknowledge its receipt and notify the manufacturer submitter of the date of the receipt. The date that the agency receives the new infant formula submission is the filing date for the submission. The manufacturer

shall not market the new infant formula before the date that is 90 days after the filing date.

106.120(f) If the ~~manufacturer~~ submitter provides additional information in support of a new infant formula submission, the agency will determine whether the additional information is a substantive amendment to the new infant formula submission. If the agency determines that the new submission is a substantive amendment, FDA will assign the new infant formula submission a new filing date. FDA will acknowledge receipt of the additional information within five working days and, when applicable, notify the ~~manufacturer~~ submitter of the new filing date, which is the date of receipt by FDA of the information that constitutes the substantive amendment to the new infant formula submission.

106.121 Quality factor submission.

To provide assurance that ~~an~~ a new infant formula meets the quality factor requirements set forth in subpart E of this part, the ~~manufacturer~~ responsible party shall submit the following data and information:

106.121(a) An explanation, in narrative form, setting forth how all quality factor requirements of subpart E of this part have been met.

~~106.121(b) Records that contain the information required by proposed Sec. 106.97(a)(1)(i) and (a)(1)(ii) collected during the study for each infant enrolled in the study. The records shall be identified by subject number, age, feeding group, gender, and study day of collection.~~

~~106.121(c)(1) Statistical evaluation for all measurements, including: Group means, group standard deviations, and measures of statistical significance for all measurements for each feeding group at the beginning of the study and at every point where measurements were made throughout the study.~~

~~106.121(c)(2) Calculation of the statistical power of the study at its completion.~~

~~106.121(d) A report on attrition and on all occurrences of adverse events during the study, which shall include:~~

~~106.121(d)(1) Identification of the infant by subject number and feeding group and a complete description of the adverse event, including comparisons of the frequency and nature of occurrence in each feeding group and information on the health of the infant during the course of the study, including the occurrence and duration of any illness;~~

~~106.121(d)(2) A clinical assessment, by a health care provider, of the infant's health during each suspected adverse event;~~

~~106.121(d)(3) A complete listing of all infants who did not complete the study, including the infant's subject number and the reason that each infant left the study.~~

~~106.121(e) The results of the Protein Efficiency Ratio, in accordance with Sec. 106.97(b).~~

106.121(fb) A statement certifying of assurance that the manufacturer or responsible party has collected and considered all information and data concerning the ability of the infant formula to meet the quality factor requirements, and that the manufacturer or responsible party is not aware of any information or data that would show that the formula does not meet the quality factors requirements.

106.130 Verification submission.

106.130(a) Unless subject to 106.120(c) [proposed by IFC to be moved and become 106.140(d)], Manufacturers or responsible parties shall, after the first production and before the introduction into interstate commerce of the new infant formula, verify in a written submission to FDA at the address given in Sec. 106.110(a), that the infant formula complies with the requirements of the Federal Food, Drug, and Cosmetic Act (the act) and is not adulterated. An original and two copies of this verification shall be submitted.

106.130(b) The verification submission shall include the following information:

106.130(b)(1) The name of the new infant formula; the filing date for the new infant formula submission, in accordance with Sec. 106.120, for the subject formula; and the identification number assigned by the agency, if available, to the new infant formula submission;

106.130(b)(2) A statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula notification and for which the manufacturer or responsible party provided assurances in accordance with the requirements of Sec. 106.120;

106.130(b)(3) A summary of test results of the level of each nutrient required by §107.100 of this chapter and any nutrient added by the manufacturer in the formula, presented in units per 100 kilocalories at the final-product-stage.

106.130(b)(4) If testing for protein biological quality is needed, an assurance that the PER or other test has commenced, and that the results will be forwarded to FDA within 10 working days of their receipt by the manufacturer or responsible party as a supplement to the verification submission.

106.130(b)(45) ~~A certification that the manufacturer has~~ An assurance by the responsible party that all manufacturers have established current good manufacturing practices including quality control procedures and in-process controls, including testing required

by current good manufacturing practice, designed to prevent adulteration of this formula in accordance with subparts B and C of this part.

106.130(c) The submission will not constitute written verification under section 412(d)(2) of the act when any data prescribed in paragraph (b) of this section are lacking or are not set forth so as to be readily understood. In such circumstances the agency will notify the submitter within five working days that the notice is not adequate complete.

106.140 Submissions for Minor Changes in the Infant Formula ~~concerning a change in infant formula that may adulterate the product.~~

106.140(a) When a manufacturer makes a change in the formulation or processing of the formula that is determined to be a notifiable minor change because the manufacturer or responsible party determines it may affect whether the formula is adulterated under section 412(a) of the Federal Food, Drug, and Cosmetic Act (the act) act, it shall, before the first processing of such formula, make a submission to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies shall be submitted. 106.140(b) The submission shall include:

106.140(b)(1) The name and physical form of the infant formula (i.e., powder, ready-to-feed, or concentrate);

106.140(b)(2) An explanation of why the change ~~in formulation or processing~~ may affect whether the formula is adulterated and assurance that the formula will not be introduced into interstate commerce unless it is not adulterated;

106.140(b)(3) A submission that complies with §106.120(b)(3), (b)(4), (b)(5), and (b)(6). When appropriate, a statement to the effect that the information required by §106.120(b)(3), (b)(4), (b)(5), or (b)(6) has been provided to the agency previously and has not been affected by the changes that is the subject of this submission, together with the identification number assigned by the agency to the relevant infant formula submission, may be provided in lieu of such submission.

106.140(c) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will promptly acknowledge receipt and notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act.

106.140(d) The requirements of 106.140 do not apply to products legally exported under §801(e) of the act.

106.150 Notification of an adulterated or misbranded infant formula.

106.150(a) A manufacturer or responsible party shall promptly notify FDA in accordance with paragraph (b) of this section, when the manufacturer or responsible party has

knowledge (that is, the actual knowledge that the manufacturer or responsible party had, or the knowledge which a reasonable person would have had under like circumstances or which would have been obtained upon the exercise of due care) that reasonably supports the conclusion that an infant formula that has been processed by the manufacturer or responsible party and that has left an establishment subject to the control of the manufacturer or responsible party:

106.150(a)(1) May not provide the nutrients required by section 412(i) of the act or by regulations issued under section 412(i)(2); or

106.150(a)(2) May be otherwise adulterated or misbranded. In the case of "adulteration" based on a failure to follow GMPs, the failure must be of such a nature as to reasonably call into question the suitability of the formula. Notification shall not be required for minor or technical misbranding.

106.150(b) The notification made according to paragraph (a) of this section shall be made by telephone, to the Director of the appropriate Food and Drug Administration district office. After normal business hours (8 a.m. to 4:30 p.m.), FDA's emergency number, 202-857-8400, shall be used. The manufacturer or responsible party shall send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204, and to the appropriate Food and Drug Administration district office specified in Sec. 5.115 of this chapter.

107.1 Status and applicability of the regulations in part 107.

107.1(a) The criteria set forth in subpart B of this part describes the labeling requirements applicable to infant formula under section 403 of the Federal Food, Drug, and Cosmetic Act (the act). Failure to comply with any regulation in subpart B of this part will render an infant formula misbranded under that section of the act. Acceptable as proposed.

107.1(b) The criteria set forth in subpart C of this part describes the terms and conditions for the exemption of an infant formula from the requirements of section 412(a), (b), and (c) of the act. Failure to comply with any regulations in subpart C of this part will result in the withdrawal of the exemption given under section 412(h)(1) of the act.

107.1(c) Subpart D of this part sets forth the nutrient requirements for infant formula under section 412(i) of the act. Failure to comply with any regulation in subpart D of this part will render an infant formula adulterated under section 412(a)(1) of the act.

107.10 Nutrient Information.

107.10(a) * * *

107.10(a)(2) A statement of the amount, supplied by 100 kilocalories, of each of the following nutrients and of any nutrient added by the manufacturer:

107.240 Notification requirements.

107.240(a) Telephone report. When a determination is made that an infant formula is to be recalled, the recalling firm shall telephone within 24 hours the appropriate Food and Drug Administration district office listed in §5.115 of this chapter and shall provide relevant information about the infant formula that is to be recalled.

107.240(b) Initial written report. Within 14 days after the recall has begun, the recalling firm shall provide a written report to the appropriate Food and Drug Administration district office. The report shall contain relevant information, including the following cumulative information concerning the infant formula that is being recalled:

107.240(b)(1) Number of consignees notified of the recall and date and method of notification, including recalls required by §107.200, information about the notice provided for retail display and the request for its display.

107.240(b)(2) Number of consignees responding to the recall communication and quantity of recalled infant formula on hand at the time it was received.

107.240(b)(3) Quantity of recalled infant formula returned or corrected by each consignee contacted and the quantity of recalled infant formula accounted for.

107.240(b)(4) Number and results of effectiveness checks that were made.

107.240(b)(5) Estimated timeframes for completion of the recall.

107.240(c) Status reports. The recalling firm shall submit to the appropriate Food and Drug Administration district office a written status report on the recall at least every 14 days until the recall is terminated. The status report shall describe the steps taken by the recalling firm to carry out the recall since the last report and the results of these steps.

107.250 Termination of an infant formula recall

The recalling firm may submit a recommendation for termination of the recall to the appropriate Food and Drug Administration district office listed in §5.115 of this chapter for transmittal to the Division of Enforcement (HFS-605), Office of Field Programs, Center for Food Safety and Applied Nutrition, for action. Any such recommendation shall contain information supporting a conclusion that the recall strategy has been effective. The agency will respond within 15 days of receipt by the Division of Enforcement (HFS-605), Office of Field Programs, Center for Food Safety and Applied Nutrition, of the request for termination. The recalling firm shall continue to implement the recall strategy until it receives final written notification from the agency that the recall

has been terminated. The agency will send such notification, unless it has information, from FDA's own audits or from other sources demonstrating the recall has not been effective. The agency may conclude that a recall has not been effective if: